Practitioner's Docket No. U013469-7

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PATENT TRADEMARK OFFICE

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/US99/27481	19 NOVEMBER 1999	23 NOVEMBER 1998
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS
TITLE OF INVENTION

BONNIE **DAVIS**
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: The completion of those filing requirements that can be made at a time later than 30 months from the priority date results from the Commissioner exercising his judgment under the authority granted under 35 USC 371(d). The filing receipt will show the actual date of receipt of the last item completing the entry into the national phase. See 37 C.F.R. §1.491 which states: "An international application enters the national state when the applicant has filed the documents and fees required by 35 USC 371(c) within the periods set forth in § 1.494 and § 1.495."

CERTIFICATION UNDER 37 C.F.R. 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on this date May 18, 2001, in an envelope as "Express Mail Post Office to Addressee," Mailing Label Number EL728212993US, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

MARIA MELIAN
(type or print name of person mailing paper)

Maria Melian
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

****WARNING:*** *Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2.Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	40 - 20 =		x $ 18.00 =	$ 360.00
	INDEPENDENT CLAIMS	2 - 3 =		x $ 80.00 =	
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $270.00				
BASIC FEE**	[x] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $100.00 [x] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $690.00 [ ] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the U.S. PTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $710.00 [ ] has not been paid (37 CFR 1.492(a)(3)) ..... $1,000.00 [ ] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $860.00				
				Total of above Calculations	1050.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				- 525.00
				Subtotal	
				Total National Fee	$ 525.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				
TOTAL				Total Fees enclosed	$ 525.00

*See attached Preliminary Amendment Reducing the Number of Claims.

i. [x] A check in the amount of $525.00 to cover the above fees is enclosed.
ii. [ ] Please charge Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

**WARNING: *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [x] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [x] has been transmitted
i. [x] by the International Bureau.
Date of mailing of the application (from form PCT/IB/308): 02 JUNE 2000.
ii. [ ] by applicant on _____.
Date

4. [x] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [x] is transmitted herewith.
b. [ ] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
Date
d. [ ] will follow.

5. [x] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.
   ii. [ ] by applicant on _____. (Date)
c. [x] have not been transmitted as
   i. [x] applicant chose not to make amendments under PCT Article 19.
   Date of mailing of Search Report (from form PCT/ISA/210):
   06 APRIL 2000.
   ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [x] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [x] has not been transmitted for reasons indicated at point 5(c) above.

7. [x] A copy of the international examination report (PCT/IPEA/409)
[x] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [ ] Annex(es) to the international preliminary examination report
a. [ ] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

10. [x] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115

a. [ ] was previously submitted by applicant on _____. Date

b. [ ] is submitted herewith, and such oath or declaration

i. [ ] is attached to the application.

ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.

c. [x] will follow.

Other document(s) or information included:

11. [x] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):

a. [ ] is transmitted herewith.

b. [x] has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): 02 JUNE 2000

c. [ ] is not required, as the application was searched by the United States International Searching Authority.

d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on _____. Date

12. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:

a. [x] is transmitted herewith.
Also transmitted herewith is/are:
[x] Form PTO-1449 (PTO/SB/08A and 08B).
[x] Copies of citations listed.

b. [ ] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. [ ] was previously submitted by applicant on _____. Date

13. [ ] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [ ] FORM PTO 1595 is also attached.

_____
_____
_____

14. [x] Additional documents:
    a. [x] Copy of request (PCT/RO/101)
    b. [x] International Publication No. WO 00/30446
       i. [x] Specification, claims and drawing
       ii. [ ] Front page only
    c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
    d. [x] Other

FORM PCT/ISA/210; FORM PCT/ISA/220; FORM PCT/IB/304; FORM PCT/IB/308; FORM PCT/IPEA/401; FORM PCT/IPEA/408 FORM PCT/IPEA/409; FORM PCT/IPEA/416

15. [x] The above checked items are being transmitted
    a. [x] before 30 months from any claimed priority date.
    b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

_____
_____
_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. 12-0425 .

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[ ] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must

only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[X] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

John Richards by Reg No 30,086

SIGNATURE OF PRACTITIONER

JOHN RICHARDS
(type or print name of practitioner)

P.O. Address

c/o Ladas & Parry
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New York, N.Y. 10023

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Practitioner's Docket No. U013469-7 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[ ] In re application of: Bonnie Davis
Application No.: 09/856,282 Group No.:
Filed: May 18, 2001 Examiner:
For: DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS

[ ] *Patent No.: Issue Date:

**NOTE: Insert name(s) of inventor(s) and title also for patent Where statement is with respect to a maintenance fee payment, also insert application number and filing date, and add Box M Fee to address.*

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(c-f) and 1.27(b-d))

With respect to the invention described in
[ ] the specification filed herewith.
[x] application no. 09/856,282, filed May 18, 2001
[ ] patent no. _____ issued _____.

I. IDENTIFICATION AND RIGHTS AS A SMALL ENTITY

I hereby state that I am

(complete either (a), (b), (c) or (d) below)

(a) Independent Inventor

[ ] a below named independent inventor, and that I qualify as an independent inventor, as defined in 37 CFR 1.9(c), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, to the Patent and Trademark Office.

(b) Noninventor Supporting a Claim by Another

[ ] making this statement to support a claim by

_____

for a small entity status for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code. I hereby state that I would qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, if I had made the above identified invention.

(c) Small Business Concern

[ ] the owner of the small business concern identified below:

check one → [ ] an official of the small business concern empowered to act on behalf of the concern identified below:

Name of Concern_____
Address of Concern_____
_____and
that the above identified small business concern qualifies as a small business concern, as defined in 13 CFR 121.3-18, and reproduced in 37 CFR 1.9(d), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

(d) Non-Profit Organization

[ ] an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization _____
Address of Organization _____
_____
TYPE OF ORGANIZATION

[ ] University or Other Institution of Higher Education

[ ] Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3))

[ ] Nonprofit Scientific or Educational Under Statute of State of the United States of America

(Name of State_____)
(Citation of Statute_____)

[ ] Would Qualify as Tax Exempt Under Internal Revenue Service Code (26 USC 501(a) and 501(c) (3)), if Located in the United States of America

[ ] Would Qualify as Nonprofit Scientific or Educational Under Statute of State of the United States of America, if Located in the United States of America

(Name of State_____)
(Citation of Statute_____)

and that the nonprofit organization identified above qualifies as a nonprofit organization, as defined in 37 CFR 1.9(e), for purposes of paying reduced fees under Sections 41(a) and (b) of Title 35, United States Code.

II. OWNERSHIP OF INVENTION BY DECLARANT

I hereby state that rights under contract or law remain with and/or have been conveyed to the above identified

[x] person	[ ] concern	[ ] organization
(item (a) or (b) above)	(item (c) above)	(item (d) above)

EXCEPT, that if the rights held are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held (1) by any person who could not be classified as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, (2) any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or (3) a nonprofit organization under 37 CFR 1.9(e).

[x] no such person, concern, or organization
[ ] person, concerns or organizations listed below*

*NOTE. *Separate statements are required from each named person, concern or organization having rights to the invention as to their status as small entities (37 CFR 1.27)*

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

Full Name _____
Address _____
[ ] INDIVIDUAL [ ] SMALL BUSINESS CONCERN [ ] NONPROFIT ORGANIZATION

III. ACKNOWLEDGEMENT OF DUTY TO NOTIFY PTO OF STATUS CHANGE

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

IV. DECLARATION

(check the following item, if desired)

NOTE *The following verification statement need not be made in accordance with the rules published on October 10, 1997, 62 Fed. Reg 52131, effective December 1, 1997*

NOTE *"The presentation to the Office (whether by signing, filing, submitting, or later advocating) of any paper by a party, whether a practitioner or non-practitioner, constitutes a certification under § 10.18(b) of this chapter Violations of § 10 18(b)(2) of this chapter by a party, whether a practitioner or non-practitioner, may result in the imposition of sanctions under § 10.18(c) of this chapter. Any practitioner violating § 10 18(b) may also be subject to disciplinary action. See §§ 10.18(d) and 10 23(c)(15)." 37 CFR 1 4(d)(2).*

[ ] I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

V. SIGNATURES

(complete only (e) or (f) below)

(e)
NOTE: All inventors must sign the statement.

Bonnie Davis
Name of Inventor

(x) Bonnie L D. Date: (x) June 22, 2007
Signature of Inventor

Name of Inventor

Date: _____
Signature of Inventor

Name of Inventor

Date: _____
Signature of Inventor

(add lines for any additional inventors who must sign)

or

(f)
NOTE The title of the person signing on behalf of a concern or nonprofit organization should be specified.

Name of Person Signing _____

Title of Person _____
(if signing on behalf of a concern or non-profit organization)

Address of Person Signing _____

_____

SIGNATURE _____ DATE _____

09/856282
JC18 Rec'd PCT/PTO 1 8 MAY 2001
PCT/US99/27481

Dosage Formulations for Acetylcholinesterase Inhibitors

Field of the Invention

The present invention relates to dosage forms for cholinesterase inhibitors that will assist in obviating some of the undesirable side effects of use of such drugs and in methods of administering such drugs for this purpose.

Background of the Invention

Recently there has been considerable interest in the use of several drugs in this class including tacrine, donepezil, physostigmine, rivastigmine and galanthamine for the treatment of Alzheimer's disease. Cholinergic drugs are known to have an effect on the body's circadian rhythms and in U. S. Patent 5585375, I have claimed the use of galanthamine for treatment of jet lag. Although beneficial in some respects, circadian effects of cholinergic drugs may cause problems for care givers in cases where the patient is unable to take care of his or herself since it can result in the patient becoming active and needing attention during the night.

Summary of the Invention

The object of the present invention is to time the release of acetylcholinesterase-inhibiting medication so as to provide it on a suitable physiological schedule, for example to ensure that it can be taken while a patient is awake in the evening and will be acting at the time of expected awakening in the morning and to provide dosage forms suitable for this purpose.

From a first aspect, the present invention provides dosage forms of a pharmaceutical composition which comprise an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period. For example in one aspect such delay will be for a period of four to twelve hours so

that a dose may be administered to the patient in the evening and allow a night's sleep before the acetyl cholinesterase inhibitor becomes active in the morning. The duration of delay chosen will depend upon the exact way in which it is chosen to administer the drug. For example if it is intended to administer the drug with an evening meal taken at, say 6:30 in the evening a twelve hour delay may be appropriate if one wishes the drug to be active the following morning. If the desired time of administration is bed time, however, a six or seven hour delay may be more useful.

From a second aspect, the present invention provides a method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor, such as Alzheimer's disease, which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.

Detailed Description of the Invention

Acetylcholinesterase inhibitors of use in the present invention are those that have a central effect and have a medium duration of action (typically from 2 to 12 hours) for the treatment of diseases where acetylcholinesterase inhibiting activity in the brain is desired, especially in the treatment of Alzheimer's disease. Suitable acetylcholinesterase inhibitors will typically have a half life in the body of from 1 to 11 hours and once released from the dosage form will pass easily through the blood-brain barrier. The most suitable compounds for this purpose are galanthamine, lycoramine and their analogs wherein wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an

alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

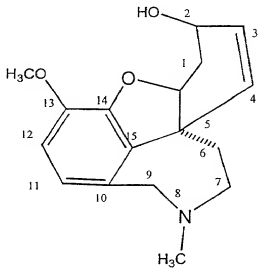
the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.

When reference is made to a substituent group, said group may be selected from alkyl or alkoxy groups of from 1 to 6 carbon atoms, halo groups, and haloalkyl groups such as trifluoromethyl.

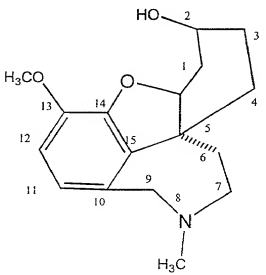
One or more of the methoxy, hydroxy and methyl groups of galanthamine or lycoramine may be replaced by the groups noted above.

Galanthamine and lycoramine have the following formulae:

Galanthamine



Lycoramine



Suitable analogs are described for example in International Patent Publication WO88/08708 and an article by Bores and Kosley in Drugs of the Future 21: 621-631 (1996). Other useful pharmacologic agents for such preparations include rivastigmine, and other pharmacologic agents with half lives of 1-11 hours.

Particularly useful analogs of galanthamine and lycoramine that are of use in the present invention include analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group, for example an alkanoyloxy or benzoyl group, of from one to seven carbon atoms or where methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from

alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Other useful analogs include compounds wherein, independently of whether or not the methoxy group has been replaced, the hydroxy group is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an acyloxy group, for example an alkanoyloxy group, typically of from 1 to 7 carbon atoms, a benzoyloxy or substituted benzoyloxy group wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups, a carbonate group or a carbamate group which may be a mono or dialkyl or an aryl carbamate or carbonate wherein the alkyl groups contain from 1 to 8 carbon atoms, preferably of from 4 to 6 carbon atoms or said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

Although a major use of the present invention will be in the treatment of Alzheimer's disease, it is also suitable for treatment of other diseases or conditions in which there is need for increased brain acetyl choline levels after a defined period. Thus it may find use, for example for healthy persons who have need for increased acetyl choline levels some specified time in the future, for example workers changing from a day shift to a night shift or vice-versa.

In Alzheimer's disease, the primary and universal neurochemical abnormality is a deficit of acetylcholine. The normal pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep. (Kametani, 1991; Mizuno, 1991) The brain content of acetylcholine exhibits a reciprocal relationship with release patterns, presumably representing stored neurotransmitter. (Saito, 1974) Likewise, acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods. (Schiebeler, 1974) Consistent with these experimental results is the long-recognized diurnal variation of human bronchial constriction from acetylcholine inhalation, being most sensitive in the evening,

when endogenous cholinergic activity would be expected to be low, and least sensitive during waking hours, when cholinergic systems would be expected to be active (Reinberg, 1974) Humans are also sensitive to the systemic administration of the acetylcholinesterase inhibitors, physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low. These disturb sleep and produce awakenings. (Sitaram, 1979, Reimann, 1994)

Animals who are made hypocholinergic either by disruption of the high affinity choline uptake system or by being raised on a false cholinergic neurotransmitter have a reduced circadian variation of acetylcholine and a disrupted diurnal rhythm of locomotor activity, which
correlates with the cholinergic hypoactivity. (Morley 1989, Szymusiak. 1993) This same situation exists in Alzheimer patients who have both cholinergic deficits and disruption of normal sleep-wake cycles. It is of major practical importance because a patient who requires twenty-four hour supervision wears out a single caretaker, requiring multiple shifts of caretakers, or institutionalization, which is expensive, frightening to the patient, and sad for the family. (see New York Times article, July 27, 1998) An additional potential utility of a dosage form which can be taken when convenient, and active when needed, would therefore be the superimposition of a physiological rhythm of cholinergic activity, via a pill, onto a brain in which the cholinergic system is deteriorating.

Preparations for treatment of Alzheimer's disease, containing cholinomimetic agents, may stimulate intestinal peristalsis as they are released, thus promoting their own passage through the gastrointestinal tract. In may therefore be useful to incorporate into the dosage unit, or to manufacture a second, similarly timed tablet, to deliver an anticholinergic agent designed to remain outside the blood brain barrier, in order to reduce gastrointestinal motility. The anticholinergic tablet might contain, for example, probanthine, 7.5-60 mg, or robinul 1 to 8 mg. A desirable formulation for an Alzheimer patient for whom sleeping hours of 11 pm to 7 am are desirable might be a pill which could be taken at bedtime and begin to release galanthamine at 5 am at a rate of 3 mg (measured as base) per hour for 4 hours, or 2 mg/hour for 6 hours beginning at 4 am. The same pill, taken at 7 am, would cover the daytime hours.

This should allow the central nervous system to become relatively hypocholinergic at the time of desired sleep, as the half life of galanthamine has been reported to be 4.5-8 hours. (Thomsen, 1990)

Alternatively, a single pill may deliver a full day's medication, although there is some risk of dumping an excessive dose, which could be dangerous in the case of cholinergic medications. The delay before release of active medication could be chosen between one and 11 hours depending on whether the pill is to be taken at dinner or bedtime.

Likely pharmacologic agents for such preparations include galanthamine, rivastigmine, and other pharmacologic agents with half lives of 1-11 hours. Dosage units for twice daily administration should contain from 4-16 mg of galanthamine (as base), or 2-10 mg of rivastigmine, both of which should be doubled in the case of once per day dosage units. Dosages for other suitable agents can be determined by standard techniques such as those set out for example in Chapter 6 (by Benjamin Calesnick) of Drill's Pharmacology in Medicine (Fourth Edition Joseph R DiPalma ed, McGraw-Hill 1971 or in Chapter 6 (by B. E. Rodda et al) of Biopharmaceutical Statistics for Drug Development (ed. Karl E. Peace, Marcel Dekker Inc, 1988). Anticholinergic agents, if needed, could be probanthine, 7.5-60 mg, to be delivered at the same time as the cholinomimetic agents, or robinul (1 to 8 mg) or similar agents incorporated so that a typical dose is delivered within the time frame of the cholinomimetic release.

Delayed action formulations for use in the present invention typically are those used for oral administration and include tablets, capsules, caplets and other convenient devices. Such dosage units may be prepared by methods well known to those skilled in the art, such as those described in Sustained Release Medications by J.C. Johnson, Noyes Data Corporation, 1980, and an article by Conte et al in Biomaterials 1993 vol 14 pages 1017 to 1023 entitled Press-coated tablets for time-programmed release of drugs, both of which are incorporated herein by reference. For example the active compounds may be coated or incorporated in a matrix which controls the elapse of between administration of the dose and the time at which release is desired.

What I claim is:

1. A dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period.

2. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.

3 A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.

4. A dosage form of a pharmaceutical composition as claimed in claim 2 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.

5. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.

6. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours

7 A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein the methoxy group thereof is replaced by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

8. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

9. A dosage form of a pharmaceutical composition as claimed in claim 1 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the N-methyl group of galanthamine or lycoramine is replaced by hydrogen, alkyl, benzyl or a cyclopropylmethyl group or a substituted or unsubstituted benzoyloxy group.

10. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

11 A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms

12. A dosage from as claimed in claim 11 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

13. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group

wherein the alkyl groups contain from 1 to 8 carbon atoms.

14. A dosage from as claimed in claim 12 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

15 A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

16 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

17 A dosage form as claimed in claim 8 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.

18 A dosage form of a pharmaceutical composition as claimed in claim 7 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group of galanthamine or lycoramine is replaced by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group.

19. A dosage form as claimed in claim 7 wherein said acetylcholinesterase inhibitor is galanthamine.

20. A dosage form as claimed in claim 1 wherein said acetylcholinesterase inhibitor is rivastigmine.

21. A method of treatment of a patient suffering from a disease or condition in which it is desirable to administer a centrally acting acetylcholinesterase inhibitor which comprises administering a dosage form of a pharmaceutical composition which comprises an effective amount of an acetylcholinesterase inhibitor wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a specified period prior to acetylcholinesterase inhibition being desired.

22. A method of treatment as claimed in claim 21 wherein said patient is suffering from Alzheimer's disease.

23 A method of treatment as claimed in claim 21 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from four to twelve hours.

24 A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from six to nine hours.

25. A method of treatment as claimed in claim 23 wherein the composition is formulated to delay the activity of the acetyl cholinesterase inhibitor for a period of from eight to twelve hours.

26 A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a duration of action of from 2 to 12 hours.

27. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor has a half life of from one to eleven hours

28 A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs of said compounds wherein at least one of the methoxy, hydroxy or methyl groups of the galanthamine or lycoramine is replaced as follows:

the methoxy group by another alkoxy group of from one to six carbon atoms, a hydroxy group, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the hydroxy group by an alkoxy group of from one to six carbon atoms, hydrogen, an alkanoyloxy group, a benzoyloxy or substituted benzoyloxy group, a carbonate group or a carbamate group;

the N-methyl group by hydrogen, alkyl, benzyl, cyclopropylmethyl or a substituted or unsubstituted benzoyloxy group.

29. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the methoxy group of such compounds is replaced by a hydrogen, hydroxy or alkoxy group of from two to six carbon atoms or an acyloxy group of from one to seven carbon atoms.

30 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

31. A method of treatment as claimed in claim 30 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

32. A method of treatment as claimed in claim 31 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the hydroxy group thereof is replaced by a mono or dialkyl carbamate or carbonate group wherein the alkyl groups contain from 1 to 8 carbon atoms.

33. A method of treatment as claimed in claim 32 wherein the alkyl group or groups of said carbonate or carbamate groups comprise from 4 to 6 carbon atoms

34 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine or lycoramine wherein the methoxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

35 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of analogs of galanthamine and lycoramine wherein the hydroxy group thereof is replaced by an aryl carbamate or carbonate group wherein said aryl group is selected from phenyl, naphthyl, substituted phenyl and substituted naphthyl groups wherein said substituent is selected from alkyl and alkoxy groups of from 1 to 6 carbon atoms, trifluoro methyl groups and halo groups.

36 A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is selected from the group consisting of galanthamine, lycoramine and analogs thereof wherein the hydroxy group of such compounds is replaced by a hydrogen or alkoxy group of from one to six carbon atoms or an acyl group of from one to seven carbon atoms.

37. A method of treatment as claimed in claim 28 wherein said acetylcholinesterase inhibitor is galanthamine.

38. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is rivastigmine.

39. A method of treatment as claimed in claim 21 wherein said acetylcholinesterase inhibitor is administered in conjunction with a compound that reduces its peripheral effects.

40. A method of treatment as claimed in claim 39 wherein said acetylcholinesterase inhibitor is administered in conjunction with a suitable dose of probanthine or robinul.

Practitioner's Docket No. U013469-7 *PATENT*

Optional Customer No. Bar Code

00140
00140
PATENT TRADEMARK OFFICE

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type:

(check one applicable item below)

[ ] original.
[ ] design.

NOTE. With the exception of a supplemental oath or declaration submitted in a reissue, a supplemental oath or declaration is not treated as an amendment under 37 CFR 1.312 (Amendments after allowance) M.P.E.P. Section 714.16, 7th Ed

[ ] supplemental.

NOTE If the declaration is for an International Application being filed as a divisional, continuation or continuation-in-part application, do not check next item, check appropriate one of last three items

[x] national stage of PCT.

NOTE If one of the following 3 items apply, then complete and also attach ADDED PAGES FOR DIVISIONAL, CONTINUATION OR C-I-P

NOTE. See 37 C.F.R. Section 1.63(d) (continued prosecution application) for use of a prior nonprovisional application declaration in the continuation or divisional application being filed on behalf of the same or fewer of the inventors named in the prior application

[ ] divisional.
[ ] continuation.

NOTE Where an application discloses and claims subject matter not disclosed in the prior application, or a continuation or divisional application names an inventor not named in the prior application, a continuation-in-part application must be filed under 37 C.F.R. Section 1.53(b) (application filing requirements-nonprovisional application)

[ ] continuation-in-part (C-I-P).

INVENTORSHIP IDENTIFICATION

WARNING: *If the inventors are each not the inventors of all the claims, an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted*

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am the original, first and sole inventor *(if only one name is listed below)* or an original, first and joint inventor *(if plural names are listed below)* of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

DOSAGE FORMULATIONS FOR ACETYLCHOLINESTERASE INHIBITORS

SPECIFICATION IDENTIFICATION

The specification of which:

(complete (a), (b), or (c))

(a) [ ] is attached hereto.

NOTE. *"The following combinations of information supplied in an oath or declaration filed on the application filing date with a specification are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F.R Section 1.63.*

"(1) name of inventor(s), and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration on filing;

"(2) name of inventor(s), and attorney docket number which was on the specification as filed; or

"(3) name of inventor(s), and title which was on the specification as filed."

Notice of July 13, 1995 (1177 O.G. 60)

(b) [ ] was filed on _____, [ ] as Application No. _____
[ ] and was amended on _____ (if applicable).

NOTE: *Amendments filed after the original papers are deposited with the PTO that contain new matter are not accorded a filing date by being referred to in the declaration. Accordingly, the amendments involved are those filed with the application papers or, in the case of a supplemental declaration, are those amendments claiming matter not encompassed in the original statement of invention or claims See 37 C.F.R. Section 1.67*

NOTE: *"The following combinations of information supplied in an oath or declaration filed after the filing date are acceptable as minimums for identifying a specification and compliance with any one of the items below will be accepted as complying with the identification requirement of 37 C.F R Section 1 63:*

(A) application number (consisting of the series code and the serial number, e g , 08/123,456),
(B) serial number and filing date;
(C) attorney docket number which was on the specification as filed;
(D) title which was on the specification as filed and reference to an attached specification which is both attached to the oath or declaration at the time of execution and submitted with the oath or declaration; or
(E) title which was on the specification as filed and accompanied by a cover letter accurately identifying the application for which it was intended by either the application number (consisting of the series code and the serial number, e.g , 08/123,456), or serial number and filing date Absent any statement(s) to the contrary, it will be presumed that the application filed in the PTO is the application which the inventor(s) executed by signing the oath or declaration.
M.P.E P Section 601 01(a), 7th ed

(c) [x] was described and claimed in PCT International Application No. US99/27481 filed on November 19, 1999 and as amended under PCT Article 19 on _____*(if any)*.

SUPPLEMENTAL DECLARATION (37 C.F.R. Section 1.67(b))

(complete the following where a supplemental declaration is being submitted)

[ ] I hereby declare that the subject matter of the

[ ] attached amendment
[ ] amendment filed on _____.

was part of my/our invention and was invented before the filing date of the original application, above identified, for such invention.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56,

(also check the following items, if desired)

[ ] and which is material to the examination of this application, namely, information where there is a substantial likelihood that a reasonable Examiner would consider it important in deciding whether to allow the application to issue as a patent, and

[ ] in compliance with this duty, there is attached an information disclosure statement, in accordance with 37 C.F.R. Section 1.98.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

NOTE "The claim to priority need be in no special form and may be made by the attorney or agent of the foreign application is referred to in the oath or declaration as required by Section 1.63. The claim for priority and the certified copy of the foreign application specified in 35 U.S.C. Section 119(b) must be filed in the case of an interference (Section 1.630), when necessary to overcome the date of a reference relied upon by the examiner, when specifically required by the examiner, and in all other situations, before the patent is granted. If the claim for priority or the certified copy of the foreign application is filed after the date the issue fee is paid, it must be accompanied by a petition requesting entry and by the fee set forth in Section 1.17(i). If the certified copy is not in the English language, a translation need not be filed except in the case of interference; or when necessary to overcome the date of a reference relied upon by the examiner, or when specifically required by the examiner, in which event an English language translation must be filed together with a statement that the translation of the certified copy is accurate." 37 C.F.R. Section 1.55(a)

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

(complete (d) or (e))

(d) [ ] no such applications have been filed.
(e) [ ] such applications have been filed as follows.

NOTE Where item (c) is entered above and the International Application which designated the U.S itself claimed priority check item (e), enter the details below and make the priority claim.

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING DAY, **MONTH**, YEAR	PRIORITY CLAIMED UNDER 35 USC 119
US	60/109,611	23 NOVEMBER 1998	[X]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO
			[ ]YES [ ]NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S)
(35 U.S.C. Section 119(e))

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

PROVISIONAL APPLICATION NUMBER **FILING DATE**

_____/_____ _____
_____/_____ _____
_____/_____ _____

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. SECTION 120

[ ] The claim for the benefit of any such applications are set forth in the attached ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART (C-I-P) APPLICATION.

ALL FOREIGN APPLICATION(S), *IF ANY,* FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

NOTE: *If the application filed more than 12 months from the filing date of this application is a PCT filing forming the basis for this application entering the United States as (1) the national stage, or (2) a continuation, divisional, or continuation-in-part, then also complete ADDED PAGES TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR DIVISIONAL, CONTINUATION OR C-I-P APPLICATION for benefit of the prior U.S. or PCT application(s) under 35 U.S.C. Section 120.*

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

JOSEPH H. HANDELMAN, 26179

JOHN RICHARDS, 31053

RICHARD J. STREIT, 25765

PETER D. GALLOWAY, 27885

IAIN C. BAILLIE, 24090

RICHARD P. BERG, 28145

JULIAN H. COHEN, 20302

WILLIAM R. EVANS 25858

JANET I. CORD, 33778

CLIFFORD J. MASS, 30086

CYNTHIA R. MILLER, 34678

(Check the following item, if applicable)

[ ] I hereby appoint the practitioner(s) associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

[ ] Attached, as part of this declaration and power of attorney, is the authorization of the above-named practitioner(s) to accept and follow instructions from my representative(s).

NOTE *"Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4)." Section 601.03, M.P.E.P., 7th Ed.*

SEND CORRESPONDENCE TO

Ladas & Parry
26 West 61st Street
New York, N.Y. 10023

DIRECT TELEPHONE CALLS TO:
(Name and telephone number)
John Richrds

(212) 708-1915

(complete the following if applicable)

Since this filing is a [ ] continuation [ ] divisional there is attached hereto a Change of Correspondence Address so that there will be no question as to where the PTO should direct all correspondence.

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

NOTE: Carefully indicate the family (or last) name, as it should appear on the filing receipt and all other document

NOTE Each inventor must be identified by full name, including the family name, and at least one given name without abbreviation together with any other given name or initial, and by his/her residence, post office address and country of citizenship. 37 C F R. Section 1.63(a)(3).

NOTE Inventors may execute separate declarations/oaths provided each declaration/oath sets forth all the inventors. Section 1.63(a)(3) requires that a declaration/oath, inter alia, identify each inventor and prohibits the execution of separate declarations/oaths which each sets forth only the name of the executing inventor. 62 Fed Reg. 53,131, 53,142, October 10, 1997,

Full name of sole or first inventor

Bonnie M Davis
(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature (x) Bonnie M Davis

Date (x) June 22, 2001 **Country of Citizenship** United States

Residence Syosset, N.Y.

Post Office Address 160 Cold Spring Road, Syosset, N.Y. 11791

Full name of second joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

Full name of third joint inventor, if any

(Given Name) *(Middle Initial or Name)* *Family (Or Last Name)*

Inventor's signature _____

Date _____ **Country of Citizenship** _____

Residence _____

Post Office Address _____

(check proper box(es) for any of the following added page(s) that form a part of this declaration)

[ ] **Signature** for fourth and subsequent joint inventors. *Number of pages added* _____

* * *

[ ] **Signature** by administrator(trix), executor(trix) or legal representative for deceased or incapacitated inventor. *Number of pages added* _____

* * *

[ ] **Signature** for inventor who refuses to sign or cannot be reached by person authorized under 37 C.F.R. Section 1.47. *Number of pages added* _____

* * *

[ ] Added page for **signature** by one joint inventor on behalf of deceased inventor(s) where legal representative cannot be appointed in time. (37 C.F.R. Section 1:47)

* * *

[ ] Added pages to combined declaration and power of attorney for divisional, continuation, or continuation-in-part (C-I-P) application.

[ ] Number of pages added _____

* * *

[ ] Authorization of practitioner(s) to accept and follow instructions from representative.

(If no further pages form a part of this Declaration, then end this Declaration with this page and check the following item)

[x] This declaration ends with this page.